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KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF MODULATION OF INTERACTION BETWEEN RECEPTOR AND LIGAND

(57) Abstract: The present invention relates to a method for modulating the interaction between at least two proteins, wherein at least one of the two proteins is a functional cell-surface receptor and the other protein is the receptor ligand. The invention features a binding site of said functional cell-surface receptor on the receptor ligand and discloses a series of amino acid sequences, which are part of the structure of said binding site and/or involved in the interaction between the receptor and the ligand. Moreover, the present invention features methods for molecular design and screening of a candidate compound capable of modulating the interaction between the functional cell-surface receptor and receptor ligand through the described binding site, and provides a screening assay for identification of such a compound. The invention further describes an antibody capable of binding to the above binding site and/or to an epitope comprising an amino acid sequence essential for executing the receptor ligand interaction through said binding site. The invention also concerns a variety of uses of the disclosed methods, peptide sequences and antibodies. The invention in preferred embodiments concerns the binding site of the fibroblast growth factor receptor (FGFR) on FGFR ligands, compounds capable of modulating the receptor ligand interaction through said binding site, and antibody capable of recognition of said binding site.

INTERNATIONAL SEARCH REPORT

| | |
|------------------|---------------------------|
| Internal PCT/ | Application No 3/00901 |
|------------------|---------------------------|

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 G01N33/566 C07K7/00 //A61K38/00,C07K14/71

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 G01N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| P,X | WO 03 016351 A (SKLADCHIKOVA GALINA ;BOCK ELISABETH (DK); BEREZIN VLADIMIR (DK); E) 27 February 2003 (2003-02-27) See SEQ ID NO:1 | 1-44, 48-54 |
| X | WO 97 38708 A (GEN HOSPITAL CORP ;SONG HEEKYUNG (US); WANG YUYING (US); GOETINCK) 23 October 1997 (1997-10-23) page 4, line 21 -page 5, line 29; claim 24 --- -/-- | 1-44, 48-54 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Internat

Application No

PCT/EP 03/00901

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | GALINA SKLADCHIKOVA ET AL: "Extracellular adenosine triphosphate affects neural cell adhesion molecule (NCAM-mediated cell adhesion and neurite outgrowth" JOURNAL OF NEUROSCIENCE RESEARCH, vol. 57, 1999, pages 207-218, XP002284206 page 215, right column, line 1 - line 40 and especially line 17 (AENQQGUS), abstract | 1-44, 48-54 |
| A | --- WO 91 00916 A (UNIV CALIFORNIA) 24 January 1991 (1991-01-24) page 5, line 16 - line 25 page 25, line 9 | 1-44, 48-54 |
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| A | --- US 6 255 454 B1 (BARR PHILIP J ET AL) 3 July 2001 (2001-07-03) column 3, line 8 - line 30 | 1-44, 48-54 |
| A | --- LARS C. B. RONN ET AL: "Neurite outgrowth induced by a synthetic peptide ligand of neural cell adhesion molecule requires fibroblast growth factor receptor activation" JOURNAL OF NEUROCHEMISTRY, vol. 75, 2000, pages 665-671, XP002284207 the whole document | 1-44, 48-54 |
| A | --- PHILIPP NIETHAMMER ET AL: "Cosignaling of NCAM via lipid rafts and the FGF receptor is required for neuritogenesis" THE JOURNAL OF CELL BIOLOGY, vol. 157, no. 3, 29 April 2002 (2002-04-29), pages 521-532, XP002284208 ISSN: 0021-9525 the whole document | 1-44, 48-54 |
| A | --- WO 00 11204 A (LANAHAN ANTHONY A ;BENEKEN JUTTA (US); TU JIAN CHENG (US); WORLEY) 2 March 2000 (2000-03-02) the whole document | 1-44, 48-54 |
| | --- -/-- | |

INTERNATIONAL SEARCH REPORT

Internal

Application No

PCT/D 8/00901

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | FERDYNAND J KOS ET AL: "Costimulation of T cell receptor-triggered IL-2 production by Jurkat T cells via fibroblast growth factor receptor 1 upon its engagement by CD56" IMMUNOLOGY AND CELL BIOLOGY, vol. 80, 2002, pages 364-369, XP002284209 the whole document --- | 1-44, 48-54 |
| A | DATABASE EBI [Online] 1 November 1996 (1996-11-01) retrieved from EMBL Database accession no. Q61945 XP002297229 93% identity in 14aa/49aa with SEQ ID NO 9 & SANTONI, M.J. ET AL: "Differential exon usage involving an unusual slicing mechanism generates at NCAM cDNA in mous brain" EMBO J., vol. 8, 1989, pages 385-392, ----- | 1-44, 48-54 |

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/DK 03/00901

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-24
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-3, 14-25, 29-44 and 54
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-44 and 48-54 (all partly)

directed to a method of modulating the interaction between a fibroblast growth factor receptor and a protein having a binding site comprising SEQ ID NO:1 (NCAM Fn III, FGFR binding motif) and a method of finding compounds which interact with FGFR and a polypeptide comprising the sequence SEQ ID NO: 1.

Invention 2: 1-54 (all partly)

directed to a method of modulating the interaction between a fibroblast growth factor receptor and a protein having a binding site comprising SEQ ID NO2 (Interleukin-6 receptor beta chain, FGFR binding motif) and a method of finding compounds which interact with FGFR and a polypeptide comprising the sequence SEQ ID NO: 2.

Inventions 3-146: claims 1-54,
all partially and as far as applicable.

Subject-matter essentially as defined above for invention 2, but limited to the respective SEQ.ID s 3-146, whereby invention 3 relates to SEQ ID NO:2, invention 3 to SEQ ID NO:3, etc and invention 146 relates to SEQ ID NO:146.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1-24

Although claims 1- 24 are directed to a method of treatment of the human/animal body, to the extent that they pertain to in vivo use, a search has been carried out, based on the alleged effects of the compound for the parts of the claims which belong to invention 1 and which appear to be clear, supported and disclosed.

Continuation of Box I.2

Claims Nos.: 1-3, 14-25, 29-44 and 54

Present claims 1-3, 14-25, 29-44 and 54 relate to methods using a compound defined by reference to a desirable characteristic or property, namely using a compound being a functional cell-surface receptor, or using a compound comprising at least two immunoglobulin (Ig)-like domains and/or at least two fibronectin type 3 (F3) domains or at least one Ig-like and one F3 domain . Claim 22 refer to a method using a compound being a functional cell-surface receptor and another protein being characterized by having a binding site consisting of one or more "strand-loop-strand" structural motifs. Claims 1, 45 and claims dependent of these claims lack clarity because of the expression "fragments, variants or homologues thereof". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the method using fibroblast growth factor receptors and a polypeptide having a FGFR binding site comprising SEQ ID NO 1 have been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International

Application No

PCT/D/00901

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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